REMARKS

Claims 1, 2, 4-10, 13, 15, 16, and 18 are pending in the instant application. The claims as pending are attached hereto as *Appendix B*.

I. Withdrawn Rejections

Applicants note with appreciation that the rejection of Claims 1, 2, 4-10, 13, 15, and 16 under 35 U.S.C. § 112, first paragraph, for lack of written description is withdrawn.

Applicants further note with appreciation that the rejection of Claim 16 under 35 U.S.C. § 112, first paragraph, for lack of enablement with regard to the term "pharmaceutical" is withdrawn.

Applicants further note with appreciation that the previous rejection of Claims 1, 2, 4-7, 9, 10, 13, 15, and 16 under 35 U.S.C. § 112, second paragraph, as being indefinite is withdrawn.

II. The Amendments

Claims 1, 2, 4, 8, 9, and 10 have been amended, without prejudice, for the purpose of more clearly defining what Applicants regard as the invention. Applicants reserve the right to pursue canceled or amended subject matter in one or more timely filed continuation or continuation-in-part applications. The amendments do not introduce new matter and they are fully supported by the Specification of the present application and the claims as originally filed, as specified below. Therefore, entry of the amendment under 37 C.F.R. § 1.111 is respectfully requested.

More specifically, Claims 1, 4, and 9 have been amended to replace the term "joined" by "bonded," as requested by the Examiner. This amendment is supported throughout the specification and by Claims 1, 4, and 9 as originally filed. Claim 2 has been amended to obviate the Examiner's objection to the term "comprising." The amendment is supported, for example, by Claim 2 as originally filed. Claims 1, 4 and 9 have been amended to clarify the chemical nature of the recited chemical bonds. This amendment is supported in the specification and by Claims 1, 4 and 9 as originally filed. Claims 4 and 9 have been amended to clarify an inherent inconsistency. The amendment is supported by Claims 4 and 9 as originally filed. Finally, Claim 10 has been amended to recite a proper method step. The amendment is supported in the specification, for example, at page 4, lines 10-19 and Claims 1 and 10 as originally filed.

A marked-up copy of the amended claims is attached hereto as *Appendix A*. The claims as pending after entry of the instant amendments are attached hereto as *Appendix B*.

III. Rejections

A. Rejection Of Claim 2 Under 35 U.S.C. § 112, First Paragraph For Lack Of Written Description

Claim 2 is rejected under 35 U.S.C. § 112, first paragraph for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time of application. The rejections are obviated and/or overcome by the amendment to Claim 2.

Specifically, Claim 2 has been amended to replace the phrase "comprising" by the

term "is."

In view of the above, the rejection of Claim 2 under 35 U.S.C. § 112, first paragraph, for lack of written description, should be withdrawn.

B. Rejection Of Claims 1, 2, 4-10, 13, 15, 16, And 18 Under 35 U.S.C. § 112, First Paragraph For Lack Of Enablement

Claims 1, 2, 4-10, 13, 15, 16, and 18 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention.

The Examiner alleges that there is not evidence to a preferential accumulation of the claimed compounds in unhealthy tissue to allow to distinguish cancerous or inflamed tissue from healthy tissue. Applicants submit herewith a Declaration pursuant to 37 C.F.R. § 1.132 of Dr. Hannsjörg Sinn (hereinafter the "Sinn Declaration"), setting forth experiments providing clear evidence for preferential accumulation of the claimed conjugates in cancerous or inflamed tissue. The Sinn Declaration is attached hereto as *Appendix C.*

First, the Sinn Declaration shows that tetra-(4-carboxyphenyl)porphine-HSA (TCPP-HSA) selectively accumulates in cancerous tissue. *See* Sinn Declaration at ¶7. Specifically, an experiment is shown involving a C6 Glioma, implanted into rat brain. For tumor visualization the animal received TCPP-HSA. The intravenously injected dose was 1 mg/kg bodyweight (correlated to porphyrin) dissolved in saline, administered 24 hours before brain resection. As depicted in *Exhibit 2* of the Sinn Declaration, a hematoxylin/eosin-stained microsection of the rat brain shows the tumor area in the right upper part of the brain. A microsection of the same area of the rat brain, irradiated with laser light (512 nm) which

visualizes the TCPP shows that only the tumor tissue takes up the TCPP-HSA. *See* Sinn Declaration at ¶7 and *Exhibit 2*.

Furthermore, the Sinn Declaration demonstrates the selective accumulation of tetra-(4-carboxyphenyl)chlorine-HSA (TCPC-HSA) in inflamed tissue. *See* Sinn Declaration at ¶8. As shown in *Exhibit 3* of the Sinn Declaration, TCPC-HSA selectively accumulates in an lymphatic node. In this experiment, for visualization of the inflamed lymphatic node the narcotized animal received TCPC-HSA. The subcutaneously injected dose was 1 mg/kg bodyweight (correlated to the chlorine) dissolved in saline, administered two hours before the surgical intervention. The picture to the left of *Exhibit 3* was taken using white light; the picture to the right was at the same position using UV-light, demonstrating that the TCPC-HSA selectively accumulated in the inflamed area. *See* Sinn Declaration at ¶8 and *Exhibit 3*.

Thus, in view of the above, the rejection of Claims 1, 2, 4-10, 13, 15, 16, and 18, under 35 U.S.C. § 112, first paragraph, for lack of enablement, should be withdrawn.

C. Rejection Of Claims 1, 2, 4-10, 13, 15, 16, And 18 Under 35 U.S.C. § 112, Second Paragraph

Claims 1, 2, 4-10, 13, 15, 16, and 18 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is in part traversed and in part obviated and/or overcome in view of the amendments to the claims.

First, the Examiner asserts that the terms in Claim 1 of "acidic amide bond" and "acidic ester" are not terms that are known. Applicants amended the claims to replace the terms to now read "amide bond" and "ester bond." It is submitted that such terms are definite

as they are generally understood in the art.

Second, the Examiner objects to the term "joined" in Claim 1. This rejection is obviated and/or overcome in view of the amendment to the claims, replacing the term "joined" by the term "bonded."

Third, the Examiner objects to the term "acridic acid" in Claim 8. This rejection is respectfully traversed. It is submitted that the term "acridic acid " is known and understood in the art. As evidenced by "Wenske Dictionary of Chemistry," "acridic acid" is a translation of the German term "Acridinsäure." *See, Appendix D.* Accordingly, the rejection is in error and should be withdrawn.

Fourth, the Examiner contends that the term "a carrier" and "a fluorescent moiety" as used in Claims 4 and 9, respectively, is inconsistent with the reference to multiple carriers or fluorescent moieties, respectively, in the same claim. This rejection is obviated and/or overcome in view of the amendment to Claims 4 and 9.

Finally, Claim 10 is found indefinite as to the process steps. This rejection is obviated and/or overcome in view of the amendment to Claim 10.

In view of the above, the rejection of Claims 1, 2, 4-10, 13, 15, 16, and 18 under 35 U.S.C. § 112, second paragraph, should be withdrawn.

CONCLUSION

In view of the above amendments and remarks, the subject application is believed to be in good and proper order for allowance. Early notification to this effect is earnestly solicited.

If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 493-4935.

The commissioner is authorized to charge any underpayment or credit any overpayment to Deposit Account No. 16-1150 (order no. 8484-077-999) for any matter in connection with this response, including any fee for extension of time, which may be required.

Respectfully submitted,

Date March 6, 2003

43,341

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Enclosures

APPENDIX A
Serial No.: 09/463,474
Marked-up Copy of the Claims

1. (Four times amended) A conjugate for distinguishing cancerous or inflamed tissue from healthy tissue comprising a fluorescent moiety and a carrier, wherein the fluorescent moiety and the carrier are [joined] bonded to one another via an [acidic] ester bond, an [acidic] amide bond or a Schiff base, and wherein said carrier is a protein.

2. (Twice amended) The conjugate of claim 13, wherein the serum albumin [comprises] is a human serum albumin.

4. (Thrice amended) A conjugate for distinguishing cancerous or inflamed tissue from healthy tissue comprising a fluorescent moiety and a [carrier] plurality of carriers, wherein [the] said fluorescent moiety and [the] said [carrier] carriers are [joined] bonded to one another via an [acidic] ester bond, an [acidic] amide bond or a Schiff base, and wherein said [carrier is a protein, and wherein the conjugate comprises a plurality of] carriers are proteins.

5. (Reiterated) The conjugate of claim 1, wherein the fluorescent moiety comprises an acid group, a hydroxyl group, an amino group or an aldehyde group.

6. (Reiterated) The conjugate of claim 15, wherein the excitation wavelength is 630 to 850 nm.

7. (Reiterated) The conjugate of claim 18, wherein the excitation wavelength is 320 to 450 nm.

8. (Three times amended) The conjugate of claim 1, wherein the fluorescent moiety comprises a porphyrin, a [chlorin] chlorine, a [bacteriochlorin] bacteriochlorine, a chlorophyll, a phthalocyanine, a carboxy cinnamic acid, [a carboxy cinnamic acid,] a carboxyfluorescein, an acridic acid, a coumaric acid, or an indocyanine green.

9. (Thrice amended) A conjugate for distinguishing cancerous or inflamed tissue from healthy tissue comprising a plurality of fluorescent [moiety] moieties and a carrier, wherein [the] said fluorescent [moiety] moieties and [the] said carrier are [joined] bonded to one another via an [acidic] ester bond, an [acidic] amide bond or a Schiff base, and wherein said carrier is a protein[, and wherein the conjugate comprises a plurality of fluorescent moieties].

10. (Thrice amended) A method of producing the conjugate of claim 1, [wherein the] comprising:

(a) reacting a fluorescent [moiety] compound with [is covalently bonded to the] a carrier [thereby forming the connector], wherein at least one activated functional group of said fluorescent compound reacts with -OH or =NH groups of said carrier, thereby forming an amide bond, ester bond or Schiff base.

13. (Reiterated) The conjugate of claim 1, wherein the protein is a serum albumin.

15. (Reiterated) The conjugate of claim 1, wherein the fluorescent moiety has an excitation wavelength of 630 nm or greater.

16. (Reiterated) A composition comprising the conjugate of claim 1 and an acceptable carrier or excipient.

18. (Reiterated) The conjugate of claim 1, wherein the fluorescent moiety has an excitation wavelength of 450 nm or less.

APPENDIX D
Serial No.: 09/463,474
Compound Examples

Gerhard Wenske

parat

Wörterbuch Chemie

Deutsch/Englisch

Dictionary of Chemistry

German/English

Weinheim · New York · Basel
Cambridge · Tokyo

VCH

Professor Gerhard Wenske
Firlestraße 4
D-81737 München

Published jointly by
VCH Verlagsgesellschaft mbH, Weinheim (Federal Republic of Germany)
VCH Publishers, Inc., New York, NY (USA)

Editorial Directors: Dr. Hans-Dieter Junge, Dipl.-Phys. Götz Jerke
Production Director: Maximilian Montkowski
Production Manager: Claudia Grössl

Library of Congress Card No. applied for

British Library Cataloguing-in-Publication Data.
A catalogue record for this book is available from the British Library

Die Deutsche Bibliothek – CIP-Einheitsaufnahme
Wenske, Gerhard:
Wörterbuch Chemie : Deutsch/Englisch = Dictionary of chemistry / Gerhard Wenske. – Weinheim ; New York ; Basel ; Cambridge ; Tokyo : VCH, 1993
(Parat)
ISBN 3-527-26429-9 (Weinheim...)
ISBN 0-89573-527-X (New York)
NE: HST

Printed on acid-free and low-clorine paper
Gedruckt auf säurefreiem und chlorarm gebleichtem Papier

Composition and data conversion: U. Hellinger, D-69253 Heiligkreuzsteinach
Printing: strauss offsetdruck Gmbh, D-69493 Hirschberg
Bookbinding: Konrad Triltsch, Druck- und Verlagsanstalt GmbH, D-97070 Würzburg
Printed in the Federal Republic of Germany

Acidimeter *n* acidimeter, acidometer
Acidimetrie *f* acidimetry
acidimetrisch acidimetric
Acidität *f* 1. acid capacity, strength of acids, acidity; 2. acid value *{GB}*; 3. sourness *{taste}*
Aciditätskonstante *f* acidity constant
Acidobutyrometer *n* acidobutyrometer
Acidobutyrometrie *f* acidobutyrometry
Acidol *n* betaine hydrochloride, lycinehydrochloride
Acidolchromgelb G *n* milling yellow
Acidolchromschwarz F *n* diamond black F
Acidoligand *m* anionic ligand
Acidoltuchrot G *n* cloth red G
Acidolyse *f* acidolysis
acidolytisch acidolytic
Acidometer *n* acidimeter, acidometer
Acidomycin *n* acidomycin
acidophil acidophilic
acidophob acidophobic
Acidum *n {pl. Acida; Lat}* 1. acid; 2. acetylsalicylic acid
Acidum boricum *n {Lat}* <H_3BO_3> boric acid *{pharm}*
Acidum carbolicum *n {Lat}* <C_6H_5OH> carbolic acid; *s.a.* Phenol
Acidum hydrochloricum *n {Lat}* hydrochloric acid *{pharm}*
acidylieren *{obs}* acylate/to,
Acker *m* field, soil, farm land
Ackerbau *m* agriculture , cultivation [of land], tillage
Ackerbauchemie *f* agricultural chemistry; chemurgy *{obs}*
Ackerbaukunde *f* agronomy
Ackerboden *m* arable land, arable soil
Ackerfrucht *f* fruit of the soil
Ackerkamille *f* wild camomile *{Matricaria camomillae}*
Ackerkrume *f* topsoil, vegetable soil *{agri}*
Ackerland *n* arable land, farm land
Ackerschädling *m* field pest, injurious insect *{agri}*
Acocantherin *n* acocantherin
Acofriose *f* acofriose
Acolytin *n* acolytine, lyaconine
Aconitalkaloide *npl* aconite alkaloids *{Aconitum napellus; e.g. aconine, indaconine, pyracomitin}*
Aconitin *n* <$C_{34}H_{47}NO_{11}$> aconitine
Aconitsäure *f* <$HOOCCH_2C(COOH)=CHCOOH$> citridic acid, 1,2,3-propenetricarboxylic acid *{IUPAC}*, aconitic (adonic, achelleic, equisetic) acid
Aconsäure *f* <$C_5H_4O_4$> aconic acid, formylsuccinic acid lactone
Acrasin *n* acrasin *{chemotactic substance in slime molds}*
Acremit *n {obs}* acremite
Acridan *n* acridane
Acridin *n* <$C_{13}H_9N$> acridine
Acridinfarbstoff *m* acridine colo[u]r, acridine dye
Acridingelb *n* acridine yellow
Acridiniumsalz *n* **/quartäres** quaternary acridinium salt
Acridinorange *n* acridine orange, basic orange, euchrysine *{3,6-bis(dimethylamino)-acridiniumchloride, DNA-complex forming}*
Acridinsäure *f* acridic acid, quinoline-2,3-dicarboxylic acid
Acridon *n* <$(C_6H_4)_2NH(CO)$> acridone *{IUPAC}*, ketodihydroacridone
Acriflavin *n* acriflavin[e], trypaflavin[e]; [eu]flavine *{pharm; mixture of 3,6-diaminoacridin and 3,6-diamino-10-methylacridinium chloride}*
Acrifolin *n* <$C_{16}H_{23}NO_2$> acrifoline *{alcaloid}*
Acrinylisothiocyanat *n* <$HOC_6H_4CH_2NCS$> allyl isothiocyanate, mustard oil
Acrit *m* acritol
Acrolein *n* *s.* Acrylaldehyd
Acroleinharz *n* acrolein resin
α-Acrose *f* α-acrose, formose, inactive fructose, DL-fructose
ß-Acrose *f* ß-acrose, DL-sorbose, inactive sorbose
Acryl- <C_3H_3O-> acryl
Acryl-Butadienkautschuk *m* polyacrylate rubber
Acrylaldehyd *m* <$CHOCH=CH_2$> 2-propenal *{IUPAC}*, acrolein, acrylaldehyde *{IUPAC}*, acrylic aldehyde, ethylene aldehyde, allyl aldehyde
Acrylalkydharz *n* acrylic alkyde resin
Acrylamid-Gel-Elektrophorese *f* acrylamide-gel electrophoresis
Acrylamid *n* <$CH_2=CHCONH_2$> acrylamide
Acrylat-Acrylnitril-Mischpolymerisat *n* acrylate-acrylonitrile copolymer
Acrylat-Butadien-Gummi *m* acrylate-butadiene rubber, ABR, acrylic rubber
Acrylat-Butadien-Kautschuk *m* *s.* Acrylat-Butadien-Gummi
Acrylat *n* <$H_2C=CHCOOM'$; $H_2C=CHCOOR$> acrylate
Acrylatkautschuk *m* polyacrylate rubber
Acrylatweg *m* acrylate pathway *{bac. physiol: lactate → lactyl → Co acrylyl}*
Acrylester *m* <$H_2C=CHCOOR$> acrylate, acrylic ester
Acrylfaser *f* acrylic fiber
Acrylfaser *f* **/modifizierte** modacrylic fiber
Acrylglas-Schutzscheibe *f* Plexiglass safety screen
Acrylglas-Sicherheitsscheibe *f* Plexiglass safety screen
Acrylglas *n* acryl[ic] glass
Acrylharz *n* acrylate resin, acrylic resin
Acrylharzlack *m* acrylic resin lacquer
Acrylhydroxamsäure *f* acrylhydroxamic acid
Acrylkautschuk *m* acrylate-butadiene rubber, ABR, acrylic rubber
Acrylklebemittel *n* acrylic adhesive
Acrylkleber (Klebstoff) *m* acrylic adhesive
Acrylkunststoffe *mpl* acrylic plastics
Acrylmischpolymer[es] *n* acrylic copolymer
Acrylnitril-Acrylat-Mischpolymerisat *n* acrylate-acrylonitrile copolymer
Acrylnitril-Butadien-Kautschuk *m* acrylonitrile-butadiene rubber